Mathematical Modeling of Two-Dose Vaccines

Undergraduate Research Thesis

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By

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Dedication

I would like to dedicate this thesis to my parents

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for all the love and support they have given me as I pursued my ambitions and goals at Ohio State. Without your advice and moral support, I could not have completed this interesting project.

Abstract

Vaccines were invented through the advancements of technology and medicine to prevent premature death caused by infectious diseases. Although vaccines are a great way to inhibit the spread of disease, their disbursement to the population is a major component of their success. Both single and multi-dose vaccines require diligent planning to immunize the population. Even today, outbreaks of vaccine-preventable diseases such as pertussis and measles still occur in the United States. The purpose of this study is to examine the dynamics of multi-dose vaccines for diseases such as pertussis, with a particular goal of identifying circumstances when multiple doses are necessary for disease control. One of the basic models used in mathematical epidemiology is called the susceptible, infected, and recovered (SIR) model. In this modeling technique, the population dynamics are studied by dividing the population into susceptible, infected, and recovered individuals. In this project we plan to analyze the dynamics of a two-dose vaccination program by introducing a new class of vaccinated individuals to the basic SIR model. We explore if it is possible to have a single dose vaccine for an infectious disease such as pertussis. Further, the disease free equilibrium and its global stability are studied as is the endemic equilibrium and its local stability. We also calculate the critical vaccination rate. This is the minimum vaccination rate needed to eliminate disease from the population. Furthermore, this study looks into the number of secondary infections caused by an infected individual. This is called the basic reproduction number and it is specific to each type of model. These results characterize the epidemiological model. In conclusion, we find that a single dose vaccine for pertussis is only effective if there is a very low waning immunity from the first dose of vaccine. In any other instance, there must be a two-dose vaccination for the disease. The model can be further expanded to multiple doses, depending on the type of disease.

1 Introduction

The average lifespan of individuals born in 1900 was less than 55 years. Today it has increased, and the average lifespan now is greater than 75 years [15]. A significant reason for this has been the great number of advancements in medicine and technology, particularly with the introduction of vaccination. In 1796, Edward Jenner created the first vaccine for smallpox from a live cowpox virus. Many scientists and doctors followed his path and were able to create more vaccines to other diseases. Likewise, Louis Pasteur developed a vaccine for rabies in 1880s. In the 1940s, a vaccine for polio was created by Dr. Jonas Salk. In the 1930s, Dr. Leila Denmark discovered a vaccine for pertussis. Vaccination has had a major effect in disease control both in the developed and developing nations. Several prominent diseases such as measles, mumps, rubella, hepatitis B, and pertussis are now preventable

with the use of such vaccines. For vaccines to be effective, they must be disbursed to the population in a timely manner. Many of the vaccines require more than one dose over a lifetime, and the planning involved in its disbursement is crucial to its success. Let us now discuss some common vaccine preventable diseases.

One of the vaccine-preventable diseases is Hepatitis-B. One in twenty people in the United States show some sign of being affected by the Hepatitis-B Virus (HBV). HBV is a significant health concern not only in the United States, but also worldwide. In the United States an estimated 4000 to 6000 new infections occur each year in adolescents and children [1]. Some patients become chronically infected, which in turn serves as a reservoir for the future spread of HBV. Immunization of all newborn children is a strong step towards eradicating HBV. There are three common forms of the HBV vaccine: Recombivax HB, Engerix-B, and Comvax. Recombivax HB and Engerix-B share a similar time line in their disbursement. For the most part both of these vaccines are administered in three doses. They are given at 0 months, 1 month, and 6 months. Comvax has a different schedule, but also is given in three doses. Comvax is given at 2 months, 4 months, and once in $12 - 15$ months [1]. HBV is unfortunately still one of the most prevalent blood-borne diseases, however it can be eradicated by the proper use of vaccines towards newborns and children.

Measles, Mumps and Rubella are three diseases that are also preventable by using the MMR vaccine. However, there still have been a few outbreaks in the United States. In fact, there was a mumps outbreak recently at The Ohio State University in 2014. From $2000 - 2012$ there have been $1,135$ reported mumps cases in the United States [3]. Measles is another serious illness. In many occurrences it has lead to severe complications as well as death. The frequently recommended vaccine strategy is a two-dose regimen. The first dose is given to infants at the age of $12 - 15$ months and the second dose is administered at $4 - 6$ years of age. The second dose is not considered to be a booster vaccine. Instead, the purpose of this dose is to provide immunity to those who do not respond to the first dose. Approximately $2 - 5\%$ of people do not develop immunity after the first dose of the MMR vaccine [3]. The most significant measles outbreak occurred in Ohio's Amish communities. A group of unvaccinated Amish missionaries had just returned from the Philippines and brought the disease with them and it spread quickly here at home [17]. Since there is little to no vaccination in these communities, measles posed to be a significant health risk for the Amish population. Interventions by the Ohio Department of Health was able to minimize these effects.

Similarly, pertussis is another example of a vaccine preventable disease. Since the 1990s there has been an increase in the number of reported pertussis cases in the United States. This has been noticed specifically among children upto the age of 19 [7]. There are many possible reasons as to why the spread of pertussis has increased, including a waning immunity in the acellular vaccine (DTaP) or possibly increased recognition of pertussis [4]. DTaP is a vaccine given to infants at birth. This protects children from pertussis, tetanus, and diphtheria. Since 2013, Tdap (the second booster shot) is usually administered in the $7th$ grade [5, 12]. Some feel that it is important to reinforce the current vaccination program and add to it another booster program for the most affected age groups [6]. Not all countries are

capable of sustaining a two-dose program for pertussis, and certainly would not be able to fund a multi-dose pertussis model [16]. So the following question arises: is it possible to create a single dose pertussis vaccination program that could replace a two-dose pertussis vaccination strategy? We find, if ω is small enough then it is possible to implement an effective single dose vaccine strategy. In this undergraduate thesis, this question will be investigated by developing and analyzing a multi-dose vaccine model, more specifically the susceptible, infected, vaccinated and recovered (SIVR) model.

2 The Model

The SIVR model used here comes from the original susceptible, infected, and removed (SIR) epidemiological model developed by Kermack and McKendrick [20]. Kermack and McKendrick's SIR model was revolutionary for its time. Today the SIR model is one of the cornerstones of Mathematical Epidemiology. While assuming constant birth and death, this model divided the population into three different classes, susceptible (S), infected (I), and removed (R). The Susceptible portion of the population were those who have not acquired the disease, Infected are the portion of the population that are infected from the disease, and Removed are those who have either recovered from the disease or have died from it. The SIR model was first used to explain great epidemiologic events such as the London Cholera Epidemic of 1865 [18]. This figure shows a flow diagram of the SIR model:

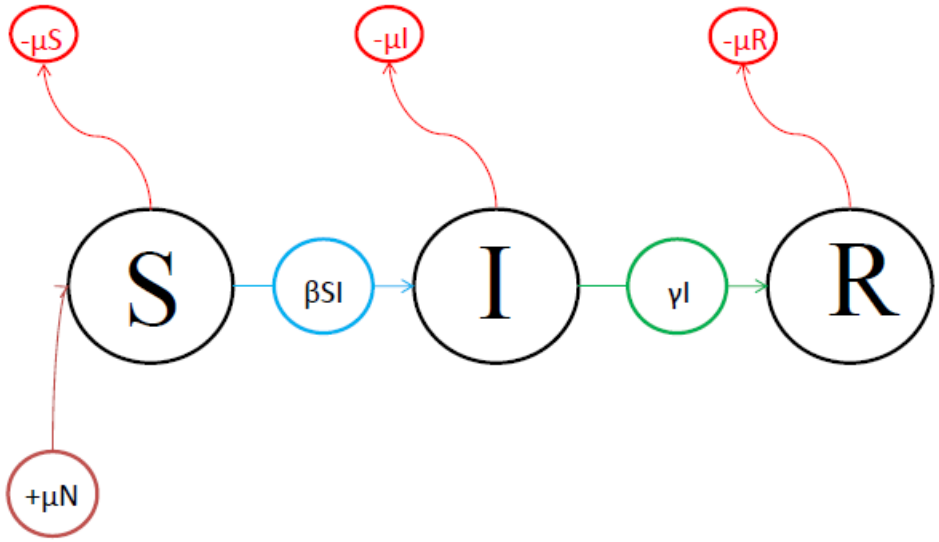

Figure 1: SIR Flow Diagram

The following differential equations characterize the basic SIR model:

$$\begin{aligned} \dot{S} &= \mu N - \beta SI - \mu S \\ \dot{I} &= \beta SI - \gamma I - \mu I \\ \dot{R} &= \gamma I - \mu R. \end{aligned} \tag{1}$$

.

The aim of this thesis is to study the dynamics of an SIR model with an additional vaccinated class. The vaccinated class contains those individuals who have gained partial or temporary immunity by receiving the first dose. The basic SIR model was modified to accommodate for a vaccinated class resulting in the SIVR model. The SIVR model problem is derived from work done on Optimal Vaccination Strategy for a two-Dose Vaccination Model by Kelly, Lenhart, Tien, and Eisenberg (personal communication, Tien). The basic framework for this model stems from Kermack and McKendrick's original SIR model [20]. In comparison to the SIR model a new "V" class of vaccinated individuals is added to the basic SIR model. This enables us to be able to study the dynamics of vaccinating a population. Like in many SIR models, this SIVR model will be treated as a compartmental ordinary differential equations (ODE) model. The model is assumed to have the same conditions of constant population size. Susceptible individuals can either be infected or vaccinated. Those who become infected later move on to the removed class. Those individuals who do get the first dose of the vaccine move to the vaccinated class at the rate of ψ. Further, if this population receives the second dose then it moves to the removed class at the rate of p. Additionally, if this population does not receive the second dose of the vaccine, then it moves back to the susceptible population at the rate of ω. The following figure is a flow diagram of the SIVR model that is the center of this thesis:

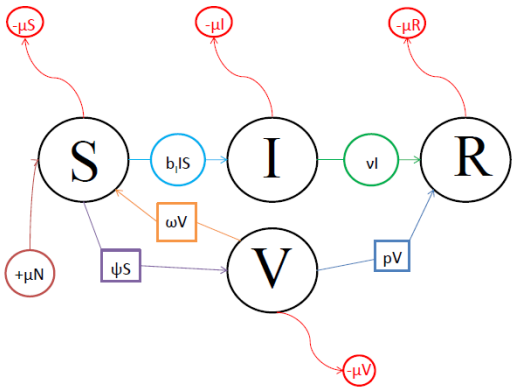

Figure 2: SIVR Flow Diagram

These are the differential equations that characterize the SIVR model:

$$\begin{aligned} \dot{S} &= \frac{dS}{dt} &&= -\mu S + \mu N - \psi S + \omega V - b_I I S \\ \dot{I} &= \frac{dI}{dt} &&= -\mu I + b_I I S - \nu I \\ \dot{V} &= \frac{dV}{dt} &&= -\mu V + \psi S - \omega V - pV \\ \dot{R} &= \frac{dR}{dt} &&= -\mu R + \nu I + pV. \end{aligned} \tag{2}$$

.

Table 1: Variables for the SIVR model

S	susceptible individual density	individuals km^{-2}
I	infected individual density	individuals km^{-2}
V	vaccinated individual density	individuals km^{-2}
R	recovered/removed individual density	individuals km^{-2}
N	total population density	individuals km^{-2}

Since we have assumed a constant population size it can be noticed that $N = S + I + V + R$.

Table 2: Parameters for the SIVR model

Parameters	Interpretation	Values/Units	Source
μ	birth and death rate	0.0035342 births and deaths/day	[10]
ψ	rate of first dose of vaccine	0.00020185263/day	[11]
$\frac{1}{\omega}$	time first dose wanes in immunity	10 years	approximated
$b_I N = \beta$	person-person contact rate	varies/day	fitting model
ν	recovery rate	0.0476/day	[10, 9]
$\frac{1}{p}$	time between first and second dose	13 years	[12]

3 Analysis of the Model

In this section we will analyze the dynamics of the SIVR model.

3.1 Disease Free Equilibrium

Finding the steady states is one of the first steps in analyzing any dynamical system. The two important states of this system of equations are the Disease Free

Equilibrium (DFE) and Endemic Equilibrium (EE). The disease free equilibrium is where there is no disease in the system. The endemic equilibrium is a state where the disease always remains present without any re-introduction of the disease. In this section we find the DFE. To do so we must set $\dot{I} = 0$ and solve. It can be seen that $S^* = \dfrac{\nu + \mu}{b_I}$ or $I = 0$. Since we are solving for the DFE here, we use $I = 0$. Later on the EE will be calculated, then $S^* = \dfrac{\nu + \mu}{b_I}$ is used to find all the steady states. Implementing $I = 0$ into our system, the equations change to:

$$\begin{array}{rrcl} (i) & \dot{S} & = & -\mu S + \mu N - \psi S + \omega V, \\ (ii) & \dot{R} & = & -\mu R + pV, \\ (iii) & \dot{V} & = & -\mu V + \psi S - \omega V - pV. \end{array} \tag{3}$$

To solve for the DFE, we set the new $\dot{S}$, $\dot{R}$, and $\dot{V} = 0$ and find the DFE. Since we have three unknowns and three equations, we use multiple substitutions to solve.

Using (ii), we have that $R = \dfrac{pV}{\mu}$.

Using (i), we have that $S = \dfrac{\mu N + \omega V}{\mu + \psi}$.

Using (iii), we have that $V = \dfrac{\psi S}{(\mu + \omega + p)}$.

Using S that we have found above, we substitute this in and simplify the expression to get

$$\begin{aligned} V &= \frac{\psi}{\mu + \omega + p} \frac{\mu N(\mu + \psi)(\mu + \omega + p)}{(\mu + \psi)[(\mu + \psi)(\mu + \omega + p) - \omega\psi]}, \\ S &= \frac{\mu N(\mu + \psi)(\mu + \omega + p)}{(\mu + \psi)[(\mu + \psi)(\mu + \omega + p) - \omega\psi]}. \end{aligned}$$

3.2 Basic Reproduction Number

R_0 is the basic reproduction number of a disease and is a critical component of any epidemiological model. This is also characterized as the number of secondary infections created from a single infection. By analyzing the value of R_0 we can make a claim if the disease will spread within a population or if it will go to extinction. If $R_0 > 1$ we find the DFE is unstable and the disease persists, and if $R_0 \leq 1$ then the DFE is stable and it dies out (Theorem 2 in [8]). To gain more insight, R_0 is calculated for the SIVR model in this project. The calculation is completed using the next generation matrix method found in [8]. To implement this method, we take that $\dot{I}$ as the only equation carrying infected individuals and the "V" class does not contribute any infections. We will will notice that this closely resembles the SIR model. Under these conditions, we formulate $\mathscr{F}$, the rate of appearance of new infections in compartment, and $\mathscr{V}$, the rate of transfer of infected individuals in and out of compartment.

For the SIVR model we have that $\mathscr{F} = b_I IS$ and $\mathscr{V} = I(\mu + \nu)$.

Then, by taking the derivative with respect to I, we have that

$F = b_I S$ and $V = \mu + \nu$. Further, we find that $V^{-1} = \dfrac{1}{\mu + \nu}$.

From [8] we know that R_0 is calculated finding the spectral radius of (FV^{-1}), also written as $R_0 = \rho(FV^{-1})$. This is done by finding the eigenvalue of FV^{-1} [8]. Applying this to the model in this project, it is found that:

$\rho(FV^{-1}) = \rho(\dfrac{b_I S}{\mu + \nu})$.

As we assume that there is no vaccination, then it is the case that $S = N$ at the DFE. So, we find that $R_0 = \dfrac{b_I N}{\mu + \nu}$. Interestingly, we see that this is exactly the same as the R_0 of an SIR model due to the fact that there is no vaccination.

3.3 Endemic Equilibrium

As mentioned previously, there are two steady states, the DFE and EE. In this section, the EE is solved for.

By setting $\dot{I} = 0$ it can be seen that $S^* = \dfrac{\nu + \mu}{b_I}$ or $I = 0$. To solve for the EE, we use S^*. Before we do so, we can take a moment to realize that $\dfrac{S^*}{N} = \dfrac{1}{R_0}$. We will discuss this later on. Let us continue to calculate the EE.

Knowing $S^* = \dfrac{\nu + \mu}{b_I}$, we set $\dot{V} = 0$ and solve for V^*:

$$V^* = \psi \left[\frac{\dfrac{(\nu + \mu)}{b_I}}{(\mu + \omega + p)} \right]$$

Likewise, we set $\dot{R} = 0$ and solve for I^* and R^*, giving

$$I^* = -\frac{\mu}{b_I} + \frac{\mu N}{(\nu + \mu)} - \frac{\psi}{b_I} + \frac{\omega\psi}{b_I(\mu + \omega + p)},$$

$$R^* = \frac{\nu}{\mu}\left[-\frac{\mu}{b_I} + \frac{\mu N}{(\nu + \mu)} - \frac{\psi}{b_I} + \frac{\omega\psi}{b_I(\mu + \omega + p)} \right] + \frac{p}{\mu}\left[\psi \frac{\dfrac{(\nu + \mu)}{b_I}}{(\mu + \omega + p)} \right].$$

We can parametrize these steady states I^*, V^*, and R^* in terms of R_0. This is accomplished in a later section. Once we have completed solving for the steady states we arrive at the endemic equilibrium for the SIVR model, written as (S^*, I^*, R^*, V^*).

If we compare these steady states with those of the SIR model, we observe that S^* is very similar. Likewise, we see a resemblance in the other steady states as well. This is logical, as the SIVR model is quite similar to the SIR model.

3.4 Local Stability of Endemic Equilibrium

To further the analysis of the dynamical system we analyze the stability of the endemic equilibrium. To do so, the system of equations is linearized and evaluated at the fixed point (where $\dot{S} = \dot{I} = \dot{V} = \dot{R} = 0$). In a one dimensional system, we evaluate the derivative of the function at the fixed point. The resulting slope is either positive or negative. If it is positive then this shows that a small perturbation will grow exponentially and if it is negative then the perturbation decays. This studies the local stability of the fixed point ([13], pages 24-25). In the SIVR model we have a three dimensional system (since R is decoupled from S, I, and V). The three dimensional linearization analog is attained through the Jacobian. As a result, we have a 3 x 3 Jacobian matrix. If the real parts of the eigenvalues are found to be less than zero, then this shows that the point is locally stable ([14], pages 233-235). The Jacobian of the SIVR model is computed below:

$$J = \begin{vmatrix} -\mu - \psi - b_I I & -b_I S & 0 & \omega \\ b_I I & -\mu + b_I S - \nu & 0 & 0 \\ 0 & \nu & -\mu & p \\ \psi & 0 & 0 & -\mu - \omega - p \end{vmatrix}$$

The next step is to evaluate the Jacobian at the endemic equilibrium (S^*, I^*, R^*, V^*) found in the preceding section and find the eigenvalues of J by solving $det(J - \lambda * Id) = 0$ for λ.

After the completing the calculation we simplify the characteristic equation as such:

$\lambda^3 + \lambda^2\alpha_1 + \lambda\alpha_2 + \alpha_3 = 0,$

where

$\alpha_1 = 2\mu + \omega + p + b_I I + \psi$

$\alpha_2 = \mu^2 + \omega\mu + p\mu + \mu\psi + p\psi + b_I\mu I + b_I\nu I + \mu b_I I + \omega b_I I + p b_I I$

$\alpha_3 = \mu^2 b_I I + \mu b_I \nu I + \omega b_I \mu I + \omega b_I \nu I + p b_I \mu I + p b_I \nu I.$

To guarantee the real parts of the eigenvalues are less than zero for a 3 x 3 system, the following criteria must be met: $\alpha_1 > 0$, $\alpha_3 > 0$, and $\alpha_1\alpha_2 > \alpha_3$ ([14], pages 233-235). It can be noticed that α_1 consists of five non-negative terms, α_2 consists of ten non-negative terms, and α_3 consists of eight non-negative terms. As we multiply α_1 by α_2 we find that it is equal to $\alpha_3 + \Lambda$, where Λ is the remaining positive terms. Then, we see that $\alpha_1\alpha_2$ - $\alpha_3 = \Lambda > 0$. So, $\alpha_1\alpha_2 > \alpha_3$. Since the criteria for the Routh-Hurwitz Stability criterion are met and the real parts of the eigenvalues are less than zero, this is stable in a local environment around the

endemic equilibrium. This implies that if there is a small perturbation away from this point, then the system will move back to the endemic equilibrium. This criteria does not make an assertion on its Global Dynamics.

3.5 Critical Vaccination Rate

Vaccinating an entire population for a specific disease is not always possible and is financially difficult to do. We find that it is possible to vaccinate less than the entire population and still drive the disease to extinction. The critical vaccination rate is the smallest rate of people that must be vaccinated to accomplish this goal. If $\psi < \psi_{crit}$, then the disease converges to the EE.

To find the critical vaccination rate we solve for ψ from the Endemic Equilibrium for $I = 0$.We find that

$$\psi_{crit} = \mu \frac{\mu + \omega + p}{\mu + p} (R_0 - 1).$$

If $R_0 < 1$ then there is no need to vaccinate anyone. This makes sense, because if $R_0 < 1$ then the disease will never spread. So, there is a need to vaccinate the population if $R_0 > 1$, because then the disease will spread. The critical vaccination rate for an SIR model is: $\psi_{crit} = \mu(R_0 - 1)$. Both critical vaccination rates are very similar, the difference lies in the factor of $\frac{\mu + \omega + p}{\mu + p}$. This is fraction is greater than one. However, if ω is very small then,

$$\frac{\mu + \omega + p}{\mu + p} \approx= \frac{\mu + p}{\mu + p} = 1.$$

Then the critical vaccination rate of the SIVR model is approximately the same as that of the SIR model if the waning immunity of the vaccine is small. Further analysis of this case is conducted in the conclusion of this thesis.

3.6 Re-Parametrize the Equations

To further our understanding of this dynamical system we non-dimensionalize the differential equations. By doing this we are able to see important groupings of parameters such as R_0.

Let $W = \frac{S}{N}$, $X = \frac{I}{N}$, $Y = \frac{R}{N}$, $Z = \frac{V}{N}$, and $l = b_I N$. Then the corresponding differential equations are

$$\begin{array}{rcrcl} \frac{dW}{dt} & = & \frac{1}{N} * \frac{dS}{dt} & = & -\mu W + \mu - \psi W + \omega Z - lXW \\ \frac{dX}{dt} & = & \frac{1}{N} * \frac{dI}{dt} & = & -\mu X + lXW - \nu X \\ \frac{dZ}{dt} & = & \frac{1}{N} * \frac{dV}{dt} & = & -\mu Z + \psi W - \omega Z - pZ. \\ \frac{dY}{dt} & = & \frac{1}{N} * \frac{dR}{dt} & = & -\mu Y + \nu X + pZ \end{array} \tag{4}$$

Now we re-scale the parameters to $R_0 = \frac{b_I N}{\mu + \nu} = \frac{l}{\mu + \nu}$. In this process we introduce new parameters:

$$a = \frac{\psi}{\mu + \nu},\ b = \frac{\mu}{\mu + \nu},\ c = \frac{\omega}{\mu + \nu},\ d = \frac{\nu}{\mu + \nu},\ f = \frac{p}{\mu + \nu}.$$

Here we are scaling time with respect to the infectious period $(\mu + \nu)$, where $\tau = (\mu + \nu)t$. Now we have:

$$\dot{W} = \frac{dW}{d\tau} = -W(a + b) + b + cZ - R_0 XW$$
$$\dot{X} = \frac{dX}{d\tau} = -X + R_0 XW$$
$$\dot{Z} = \frac{dZ}{d\tau} = -bZ + aW - cZ - fZ$$
$$\dot{Y} = \frac{dY}{d\tau} = -bY + dX + fZ$$

Then we calculate the equilibrium points again, by the same technique as earlier. We find that:

$$W^* = \frac{1}{R_0}$$
$$X^* = b + \frac{ca}{R_0(b + c + f)} - \frac{b}{R_0} - \frac{a}{R_0}$$
$$Z^* = \frac{a}{R_0(b + c + f)}$$
$$Y^* = \frac{d}{b}\left(b + \frac{ca}{R_0(b + c + f)} - \frac{b}{R_0} - \frac{a}{R_0}\right) + \frac{a}{R_0(b + c + f)}\left(\frac{f}{b}\right)$$

Similarly we compute the critical vaccination rate in terms of the new variables. From X^* we solve for a, then:

$$a_{crit} = a = b\frac{b + c + f}{b + f}(R_0 - 1).$$

The DFE is also calculated for this reparameterized version of the model:

$W^* = \frac{b}{(a + b) - \frac{ca}{b + c + f}}$ and

$$Z^* = \frac{a}{b+c+f}\left(\frac{b}{(a+b)-\frac{ca}{b+c+f}}\right).$$

3.7 Global Stability at the DFE for $R_0 \leq 1$

Earlier we calculated the EE and made an assertion about its local stability. Here we are trying to explore the global stability of the DFE. Global stability is a much stronger condition than local stability. It says that it the system converges to a specific point regardless of the initial condition, whereas local stability can only comment about the local environment of a steady state.

Let $s = \frac{S}{N}$, $i = \frac{I}{N}$, $v = \frac{V}{N}$, and $b_I N = \beta$. Then

$$\begin{aligned} \dot{s} &= -\mu s + \mu - \psi s + \omega v - \beta i s, \\ \dot{i} &= -\mu i + \beta i s - \nu i, \\ \dot{v} &= -\mu v + \psi s - \omega v - p v \end{aligned} \tag{5}$$

We only look at $\dot{s}$, i, and $\dot{v}$ since $\dot{r}$ is decoupled from the other equations. By making this parametrization, we also know that s, i, and v are ≤ 1. To analyze the global stability of this dynamical system let us first look at the these parametrized equations in the s and v plane. For $R_0 \leq 1$ our inclination is that the i equation will go to the set $i = 0$. To show this, we must rule out any periodic solutions. This can be achieved by using a Liapunov function or Dulac's Criterion among other techniques. To show that the set will converge to $i = 0$, we consider a Liapunov function. A Liapunov function is a continuously differentiable, real valued function $F(x)$ where $F(x) > 0$ for all $x \neq x^*$ and $F(x^*) = 0$. Furthermore, $\dot{F} < 0$ for all $x \neq x^*$. If these conditions are satisfied, then we can say that x^* is globally stable for all initial conditions ([13], pages 151-152). For this model we consider a Liapunov function whose form comes from Theorem 5.1 in [2].

Let

$$F = \frac{1}{\mu+\nu} i. \tag{6}$$

Then,

$$\dot{F} = -\frac{\mu}{\mu+\nu} i + \frac{\beta}{\mu+\nu} i s - \frac{\nu}{\mu+\nu} i. \tag{7}$$

By further simplifying this, we get

$$\dot{F} = i(R_0 s - 1). \tag{8}$$

It can be easily seen that $F = 0$ at s^* and i^* and $F > 0$ for all other values of s and i. Furthermore, we see that $\dot{F} \leq 0$, $R_0 \leq 1$, and $\dot{s} \leq 1$. Since this is a Liapunov function and since this is a decreasing and bounded function we can say that this will converge to the set where $i = 0$. Knowing that $i = 0$, the equations at the beginning of this section are re-evaluated. Then we achieve the following set of equations

$$\begin{aligned} \dot{s} &= -\mu s + \mu - \psi s + \omega v \\ \dot{v} &= -\mu v + \psi s - \omega v - pv. \end{aligned} \tag{9}$$

Further exploration of the global stability of this system is completed using Dulac's Criterion. For a planar vector field, Dulac's Criterion says that let $\dot{x} = f(x)$ be continuously differentiable. If there exists a continuously differentiable, real-valued function $g(x)$ such that $\nabla(g\dot{x})$ maintains only one sign on a simply connected set, then there are no periodic orbits in this set ([13], pages 203-204). Let us consider

$$\nabla(g\dot{x}) = \frac{\partial}{\partial s}(g\dot{s}) + \frac{\partial}{\partial v}(g\dot{v}) \tag{10}$$

where we take $g = 1$.

Then we have,

$$\begin{aligned} &\nabla(g\dot{x}) = \frac{\partial}{\partial s}(\dot{s}) + \frac{\partial}{\partial v}(\dot{v}) \\ &= -\mu - \psi - \mu - \omega - p < 0. \end{aligned}$$

Thus, the SIVR model is globally stable by Dulac's Criterion for $R_0 \leq 1$. This should then converge to the equilibrium regardless of any initial condition given that $R_0 \leq 1$. In this thesis we use Matlab to create simulations to better study the SIVR model. We use the initial conditions where the initial population of the S class is 0.9999, I class is 0.0001, and V class is 0 (also x-axis t represents time in days). In figure 3 we can see that the Matlab simulation reflects the theoretical results presented in this section.

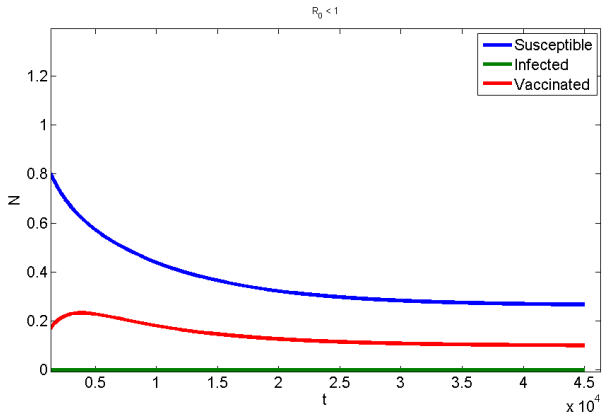

Figure 3: $\beta = 0.03, \psi = 0.00020185, \mu = 0.000035342, \nu = 0.0476, p = (1/4380), \omega = (1/3650)$ For $R_0 < 1$ the SIVR model converges to the DFE as suggested by the theoretical results

The presence of a vaccinated class in the SIVR model poses a difficulty in proving global stability of the endemic equilibrium for $R_0 > 1$. This question may be of interest to look into in the future. It is attempted to make an observation on this matter by observing the Matlab simulation for $R_0 > 1$, specifically $R_0 = 5.5$ [19]. In figure 4, we compute the simulation with $R_0 > 1$ and $\psi > \psi_{crit}$. This does not converge to the EE, but to the DFE. This makes sense. If we are vaccinating at a rate higher than the critical vaccination rate, then it should converge to the DFE.

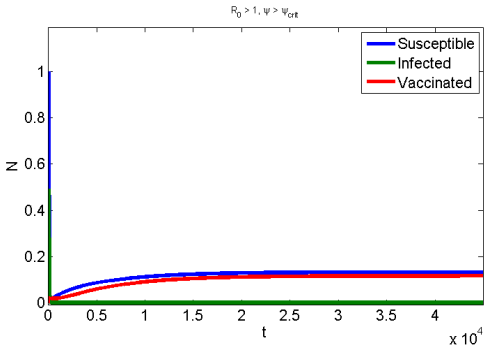

Figure 4: $\beta = 0.261994381, \psi = 0.000471498, \mu = 0.000035342, \nu = 0.0476, p = (1/4380), \omega = (1/3650)$ For $\psi > \psi_{crit}$ the simulation suggests that the SIVR model converges to the DFE

In figure 5, the simulation is run again, but this time $R_0 > 1$ and $\psi < \psi_{crit}$.

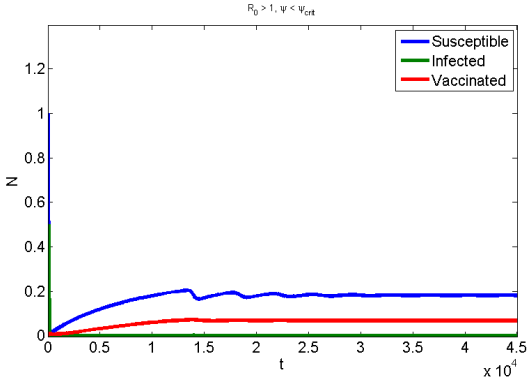

Figure 5: $\beta = 0.261994381, \psi = 0.00020185, \mu = 0.000035342, \nu = 0.0476, p = (1/4380), \omega = (1/3650)$For $\psi < \psi_{crit}$ the simulation suggests that the SIVR model converges to the EE

Looking at this case, it can be said that this converges to the endemic equilibrium. However, we can not say this for all cases $R_0 > 1$. This makes sense as we are vaccinating at rate less than the critical vaccination rate. However, we do not have

any theoretical results to affirm these claims. A Liapunov function may be created to show this, however we did not pursue this in this thesis.

4 Conclusion and Summary

Here our aim is to complete the analysis of the model and attempt to answer the question centered around this project. Is it better to have a two-dose pertussis vaccination program? Is there any way to create a single dose schedule for pertussis to reduce the financial burden in sustaining a booster program? We use matlab to better answer these questions. Using data from [9], [10], and [11] we are able to run simulations that give us a better insight. This first graphic shows use of a two-dose vaccination program.

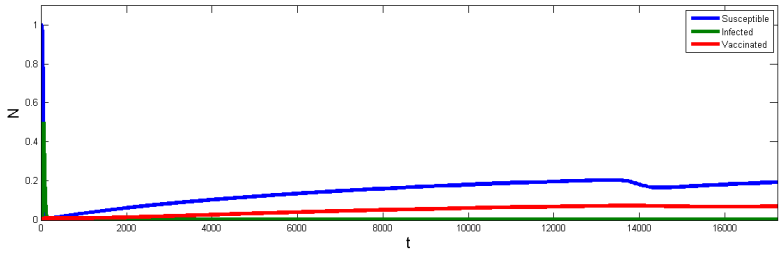

Figure 6: $\beta = 0.261994381, \psi = 0.00020185, \mu = 0.000035342, \nu = 0.0476, p = \frac{1}{4380}, \omega = \frac{1}{3650}$

We modify our SIVR model and let the parameter p (the second dose of the vaccine) equal to 0. This creates a single dose vaccine. We again run the matlab simulation and compare it with the previous simulation.

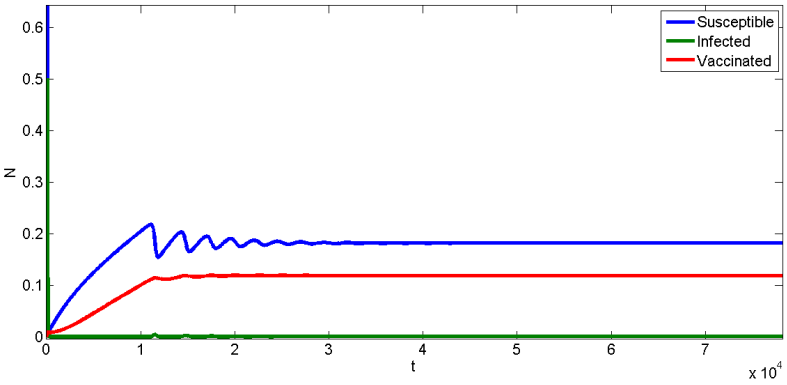

Figure 7: $\beta = 0.261994381, \psi = 0.00020185, \mu = 0.000035342, \nu = 0.0476, p = 0, \omega = \frac{1}{3650}$

It can be noticed that a two-dose pertussis schedule produces less infected individuals than the single dose pertussis schedule. Given the data that was used it easy to say that it is a better idea to implement a two-dose pertussis program. The question still persists, when will it be possible to have a single dose pertussis program. As we look back at the $\dot{V}$ equation we see that ψ, ω, and p all influence the population of the V-class, where ω is the waning immunity. Let us consider a situation where we have $p = 0$ and a small enough ω.

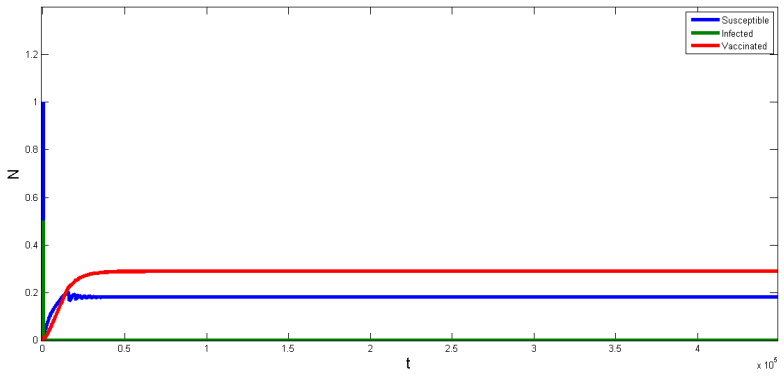

Figure 8: $\beta = 0.261994381, \psi = 0.00020185, \mu = 0.000035342, \nu = 0.0476, p = 0, \omega = (1/10950)$

It can be noticed that it may be possible to create a single dose vaccine for pertussis and still drive the disease to extinction. Let us take a look at the critical vaccination rate under these conditions. This is the critical vaccination rate where $p = 0$.

$$\psi_{crit} = (\mu + \omega)(R_0 - 1)$$

Further if ω is negligibly small, then we have

$$\psi_{crit} \approx (\mu)(R_0 - 1)$$

Here we are able to recover the original critical vaccination rate of an SIR model. Our model begins to look like the original SIR model which we know is globally stable. This suggests that it may be possible to implement a one dose vaccine for pertussis if ω is small enough. Literature [6] suggests that the first dose is waning in immunity. So if a strong first vaccine is created whose immunity does not wane (has a very small ω value), then it is possible to implement a one-dose vaccine for pertussis. A natural question arises. What can be done to reduce ω ? There may be many possible answers that may accomplish this goal. I think the development of a stronger vaccine is one way to reduce the value of ω.

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